

REMARKS

At the outset, applicants respectfully traverse the finality of the Office Action of October 8, 2008, and request that such finality be withdrawn for the reason set forth below, whereby the present amendment will be entered as a matter of right.

In the preceding Office Action, namely the Office Action mailed March 28, 2008, claim 3 was not rejected on the basis of obviousness under Section 103. In this regard, applicants accordingly amended claim 1 to incorporate the dependent portion of claim 3, thereby converting claim 1 into the equivalent of claim 3 rewritten in independent form, and such an amendment was made to obviate the rejection under Section 103.

The rejection so obviated appears at page 11 of the Office Action of March 28, 2004, and is stated as follows:

Claims 1, 7, 8, 10, 18, 19 and 21 are rejected under 35 USC 103(a) as being unpatentable over Yamamoto et al (U.S. patent application publication 2003/0211166, published November 13, 2003, cited in PTO-892) in view of Schense et al (U.S. patent application publication 2003/0012818, January 16, 2003, cited PTO-892).

Now, in the final Office Action, the rejection, not made against claim 3 earlier, is now repeated against claim 1 which corresponds to previous claim 3. This thus constitutes a new rejection of a claim previously not rejected on this basis, and without any amendments having been made which would necessitate such a new rejection.

Therefore, making the present Office Action final was improper, and such finality should be withdrawn. It is again respectfully requested that the finality of the Office Action of

October 8, 2008, on the basis of such a new rejection not necessitated by any amendment.

The Office Action of October 8, 2008, and the prior art relied upon therein, including that newly cited, have been carefully reviewed. The claims in the application are claims 4-8 and 24-27, and new claims 31-36, with claim 31 replacing previous claim 1. Applicants respectfully submit that applicants' claims define patentable subject matter warranting their allowance. Favorable reconsideration, withdrawal of the finality of the Office Action, and allowance are earnestly solicited.

A typographical or clerical error has been found in paragraph [0078] of the specification, i.e. the Figure referred to should be Fig. 5 instead of Fig. 1. this has been corrected above.

All the previous rejections based on Section 102 have been withdrawn, whereby applicants understand that applicants' claims pending as of the time of the Office Action of October 8, 2008, were deemed novel by the PTO.

A number of amendments have been presented above in the rewriting of claim 1 as new claim 31, including reciting the presence of "a crosslinking agent" in step a), and adding the phrase "wherein steps b) and c) are carried out in a spray drying procedure".

In addition, claim 31 includes definitions of the terms "polysaccharide derivative" and "crosslinking agent". This amendment

is based on the description in paragraphs [0031] to [0034], [0037], and [0042] to [0046] of the subject specification.

Regarding formula (I), applicants have added the following groups to the definition of  $X_2$  disclosed in paragraph [0033] of the subject specification:

-NHCO- $(CH_2)_4$ -CONH-NH-C(=NH)- $(CH_2)_3$ -SH,  
- $(CH_2)_2$ -NH-C(=NH)- $(CH_2)_3$ -SH, or  
- $(CH_2)_2$ -O- $(CH_2)_2$ -O- $(CH_2)_2$ -NH-C(=NH)- $(CH_2)_3$ -SH

The groups correspond to the description in paragraph [0028] of the subject specification. Namely, the groups are derived from adipic acid dihydrazide (ADH), ethylendiamine, and ethylene dioxy bisethylamine, each of which is reacted with 2-iminothiolane.

New claims 32-36 are added to take the place of those canceled. The recitations of claims 32 and 36 are based on, for example, the description in paragraph [0009] of the subject specification. The recitation of claim 34 is based on the experimental result shown in Figure 5. The recitations of claims 35 and 36 are based on, for example, the description in paragraph [0079] of the present specification.

Claims 1, 2, 4-8 and 22-30 have been rejected under Section 103 as obvious from Yamamoto in view of Schense for the reasons previously applied against claim 1 but not against claim 3, whereby this is a new rejection not necessitated by any amendment in view of the incorporation of claim 3 into claim 1 as explained above. The rejection is respectfully traversed.

It will be noted that steps b) and c) in claim 31 at present call for, and called for in claim 1 previously, dispersing the solution

by spraying to form microparticulate droplets, and concentrating the solution contained in the droplets to facilitate crosslinking. Thus, in the claimed method, the crosslinking reaction of the polysaccharide derivative is carried out in the microparticulate droplets produced by spraying of the reaction solution during forming of the microspheres.

This is one of the key technical features of the present invention, and it is neither shown nor made obvious, by either Yamamoto or Schense. As neither reference shows or makes obvious this feature, no combination of the two reference together, even if such a combination were obvious, could reach the subject matter of previous claim 1 or new claim 31 which replaces claim 1.

This important distinction is not overlooked in the rejection which states that Yamamoto discloses crosslinking agents co-formulated into microspheres, with the hyaluronic acid starting material being "partially crosslinked to aid particle formation, and the crosslinking in both non-hydrated and partially hydrated states", referring to Yamamoto at page 2, paragraph 30. The PTO therefore concludes that "the broader disclosure of Yamamoto... encompasses the crosslinking reaction occurring during the spray drying procedure..., and the disclosed embodiment does not constitute teaching away from the broader disclosure."

Respectfully, such a conclusion is unwarranted and improper in that it takes a generic disclosure and applies it to a specific instance which is not disclosed. Such an approach is never correct.<sup>1</sup> A generic disclosure does not anticipate a new species.

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<sup>1</sup> A simple example shows why this approach is not correct. Suppose that inventor A is the first to invent any alcohol, and in particular methanol. As the first inventor of any alcohol, he broadly discloses that he is the inventor of "alcohol". Inventor B comes along and invents ethanol (or any other alcohol). By the reasoning of the rejection, inventor B or any one else could never get a patent on a second alcohol in view of the broad disclosure of inventor A of alcohol. This is clearly incorrect.

Not only does Yamamoto not disclose or make obvious what applicants have specifically claimed, but Yamamoto leads the person of ordinary skill in the art in a different direction, noting for example paragraph [0030] of Yamamoto which states as follows:

The microspheres may be crosslinked using a number of different chemistries, for example the use of a carbodiimide crosslinking agent. Agents to aid crosslinking may also be co-formulated into the microspheres. (Emphasis added)

It is very clear that this description only states that the microspheres, which are already formed, may then be subjected to a crosslinking reaction, and that agents to aid crosslinking may also be co-formulated into the already formed microspheres. Further, this Yamamoto description fully corresponds to example 3, in which a 100 mM solution of EDC was added to the microspheres fabricated in the manner of either example 1 or 2.

Yamamoto further states in paragraph [0030] as follows:

The hyaluronic acid starting material can be partially crosslinked to aid particle formation. After fabrication, method of chemically crosslinking the microspheres in a non-hydrated or partially hydrated state act to increase the microsphere density.

This description only states that partially crosslinked material can be used as a starting material of particle formation, and that after formation of the microspheres, an additional crosslinking reaction is carried out. Namely, this description only refers to the crosslinking reaction before and after the microspheres formation, and does not include any teaching or suggestion regarding crosslinking reaction during formation of microspheres.

Therefore, it is clear that the description in paragraph [0030] of Yamamoto cannot properly be understood to refer to the

crosslinking reaction occurring in microparticulate droplets during the spray drying procedure. Further, other references cited in the Office Action also include no disclosure, no teaching, and no suggestion regarding such a crosslinking reaction.

Applicants do no see how Schense in any way makes up for the deficiencies of Yamamoto, as Schense includes neither disclosure nor suggestion relating to microparticles, and applicants understand that Schense has not been cited for such purpose. Therefore, even if the combination were obvious, respectfully denied, the reconstructed Yamamoto (reconstructed in view of Schense) would not reach even previously pending claim 1, let alone the more detailed replacement claim 31. With respect, the PTO has not established a valid *prima facie* case of obviousness, and the rejection should be withdrawn.

As previously stated, the claimed method is suitable for the efficient preparation of microparticles having an injectable size, which encapsulate drugs, in particular proteins and peptides, without jeopardizing their pharmacological activity (please refer to pages 6 and 7, paragraph [0009] of the applicants' specification). Such advantageous effects of the subject invention are not referred to at all in the cited references and are in no way expected or predicted.

Applicants firmly believe and respectfully submit that the person of ordinary skill in the art at the time the present invention was made would not have reached the claimed subject matter from a consideration of Yamamoto and Schense together, or indeed by consideration of any known prior art alone or in combination. The claimed invention now only appears to have been obvious after having read applicants' specification.

In addition to the aforementioned areas of non-obviousness, applicants have particularized what is meant by "polysaccharide derivative" in new claim 31. Applicants respectfully submit that the manner of crosslinkage as set forth in claim 31 would not have been obvious to the person of ordinary skill in the art at the time the present invention was made.

Withdrawal of the rejection is in order and is respectfully requested.

Claims 1, 2, 4-8 and 22-30 have been rejected as obvious under Section 103 from Illum et al U.S. patent application publication 2001/000765 (Illum) in view of newly cited Hubbell et al U.S. patent application publication 2002/0177680 (Hubbell). This rejection is respectfully traversed.

The situation with respect to the proposed combination of Illum in view of Hubbell is very similar to the situation discussed above with respect to the proposed combination based on Yamamoto in view of Schense, i.e. no possible combination of Illum in view of Hubbell could result in a reconstructed Illum which would reach previous claim 1 or new claim 31, even if such a combination were obvious. In other words, Illum does not disclose any crosslinking reaction which takes place in the microparticulate droplets, and Hubbell does not suggest or teach any modification in Illum to reach such an expedient. This important feature is recited in steps (b) (c) of claim 31 as it previously was in claim 1.

Accordingly, applicants respectfully repeat by reference their remarks above with respects to the rejection based on Yamamoto in

view of Schense, applying such remarks to the similar rejection based on Illum in view of Hubbell.

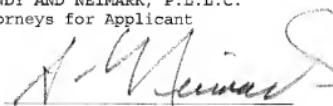
Applicants' claims would not have been obvious from the proposed combination for the reasons pointed out above, even if such combination were obvious. Withdrawal of the rejection is in order and is respectfully requested.

Applicants believe that all issues raised in the Final Action have been addressed above in a manner that should lead to patentability of the present application. If not, the finality of the Office Action should be withdrawn as being premature for the reasons provided out above. Favorable reconsideration, entry of the amendments presented above and early formal allowance are respectfully requested.

Respectfully submitted,

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